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Systematic reviews on neurodevelopmental and neurodegenerative disorders linked to pesticide exposure: Methodological features and impact on risk assessment

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abstract

Background: Epidemiological data are not currently used in the risk assessment of chemical substances in a systematic and consistent manner. However, systematic reviews (SRs) could be useful for risk assessment as they appraise and synthesize the best epidemiological knowledge available.

Objectives: To conduct a comprehensive literature research of SRs pertaining to pesticide exposure and various neurological outcomes, namely neurodevelopmental abnormalities, Parkinson's disease (PD) and Alzheimer's disease (AD), and to assess the potential contribution of SRs to the risk assessment process.

Search methods and selection criteria: Search was conducted in PubMed and Web of Science databases and articles were selected if the following inclusion criteria were met: being a SR, published until April 2015 and without language restrictions.

Data collection and analysis: For each neurological outcome, two review authors independently screened the search results for included studies. Data were extracted and summarized in two tables according to 16 criteria. Disagreements were resolved by discussion.

Main results: The total number of studies identified in the first search was 65, 304 and 108 for neurodevelopment, PD and AD, respectively. From them, 8, 10 and 2 met the defined inclusion criteria for those outcomes, respectively. Overall, results suggest that prenatal exposure to organophosphates is associated with neurodevelopmental disturbances in preschool and school children. In contrast, postnatal exposures failed to show a clear effect across cohort studies. Regarding PD, 6 SRs reported statistically significant combined effect size estimates, with OR/RR ranging between 1.28 and 1.94. As for AD, 2 out of the 8 original articles included in the SRs found significant associations, with OR of 2.39 and 4.35, although the quality of the data was rather low.

Conclusions: The critical appraisal of the SRs identified allowed for discussing the implications of SRs for risk assessment, along with the identification of gaps and limitations of current epidemiological studies that hinder their use for risk assessment. Recommendations are proposed to improve studies for this purpose. In particular, harmonized quantitative data (expressed in standardized units) would allow a better interpretation of results and would facilitate direct comparison of data across studies. Outcomes should be also harmonized for an accurate and reproducible measurement of adverse effects. Appropriate SRs and quantitative synthesis of the evidence should be performed regularly for a continuous update of the risk factors on health outcomes and to determine, if possible, dose–response curves for risk assessment.

1. Background

A systematic review (SR) is an investigation of a clearly-formulated question that uses methodological and explicit steps to identify, select and critically appraise relevant research, and to collect and analyze data found from appropriate studies. In the SR, the literature is reviewed by using a more robust and powerful systematic approach than in narrative literature reviews, thus it is less prone to biases of various kinds. Additionally, each of the studies reviewed is critically assessed for risk of bias and potential confounding factors (US-EPA, 2012). Current SRs are based on Cochrane Reviews, which consist of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-based health care (Higgins and Green, 2008).

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Data from epidemiological studies are not currently used in the risk assessment of chemical substances in a systematic and consistent manner, particularly because of the limitations of observational studies. These limitations include a lack of detailed quantitative information regarding exposure history (which hampers chemical exposure to be reliably characterized), biological plausibility of the associations found and heterogeneity of data (EFSA, 2015). However, epidemiological studies can contribute to risk assessment as part of the overall weight of evidence of the available experimental in vivo and in vitro data in order to support a causative relationship necessary for biological plausibility (Adami et al., 2011; Buonsante et al., 2014; US-EPA, 2010). Epidemiological studies can also be informative on the association between low-dose exposures and human diseases. While the most common limitation invoked for the use of these studies for human risk assessment is the lack of adequate exposure data, exposure data in animal bioassays are not necessarily more accurate as the high-to-low dose extrapolation and the animal-to-human extrapolation are major sources of error (Wright et al., 1997).

As SRs allow the identification, selection and critical evaluation of relevant information available in the open literature, they could be used by regulatory agencies to appraise and synthesize the epidemiological knowledge available for risk assessment. Ideally, SRs could contribute to substantiate the four steps of the risk assessment process (hazard identification, hazard characterization, exposure assessment and risk estimate) if relevant and robust data are available. Although the findings of SRs could provide information as input into risk assessment models, only epidemiological studies with high quality study designs and strong exposure assessment provide the most appropriate data for characterizing human risks (EFSA, 2010). Nevertheless, in most situations, current epidemiological studies may not be sufficiently robust to derive quantitative risk assessment values because of the lack of quantitative information on exposure (US-EPA, 2010).

The key characteristics of the ideal set of epidemiological evidence for risk assessment purposes should include a clear dose–response relationship, consistency across studies and biologically plausible mechanisms (EFSA, 2015). Due to the methodological rigor, objective and transparent nature of SRs, they are appropriate tools for answering well-formulated specific questions generated by the risk assessment process. When the evidence is extensive, SRs can be particularly useful in summarizing the evidence and providing more precise estimates of effects or parameters with enhanced statistical power (meta-analysis) than individual studies. Conversely, if the evidence is scarce, SRs allow knowledge gaps to be identified (EFSA, 2010).

Objectives

This paper critically appraise SRs on human neurodevelopmental and neurodegenerative disorders (Parkinson's disease — PD and Alzheimer's disease — AD) published to date in relation to pesticide exposure and considers how these SRs can impact the risk assessment process. Recommendations are proposed on how epidemiological studies can be improved for a better integration into risk assessment, in particular with a view to achieving greater uniformity in assessing the

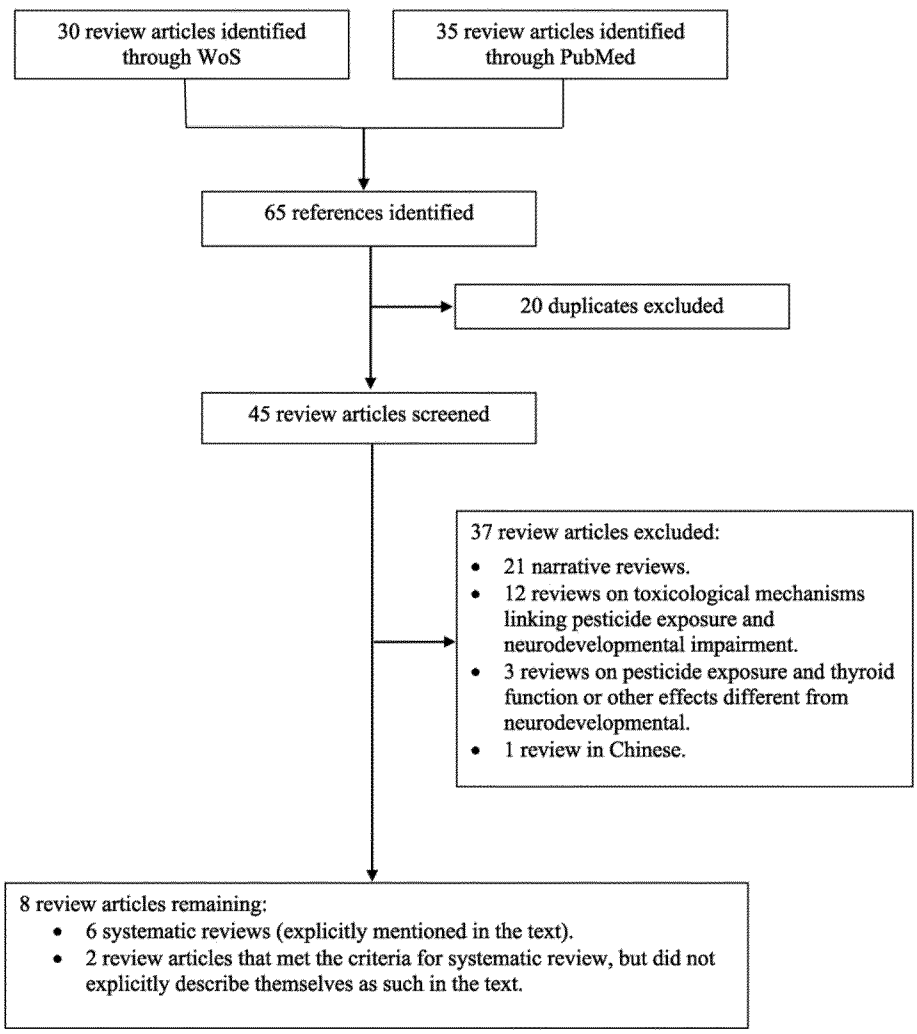

Fig. 1. PRISMA flow chart of review articles assessing pesticide exposure and neurodevelopmental effects.

Table 1
Bibliometric and methodological features of SRs evaluating neurodevelopmental effects from exposure to persistent and non-persistent pesticides.

Author (year)	Journal IF/ranking	Articles reviewed (n)	Language	Search dates (years)	Search databases	Type of study	Inclusion criteria	Methodological quality assessment
Rossignol et al. (2014)	5.62 Q1 (16/140, Psychiatry)	7 (children)	English	1976–2013	Pubmed, Scopus, EMBASE, Google Scholar, CINAHL, ERIC, AMED, PsychInfo and Web of Science	1/7 case–control (retrospective) 4/7 cohort (prospective) 2/7 cross-sectional (retrospective)	Studies exploring potential associations between estimated toxicant exposures in the environment and ASD risk. Studies measuring biomarkers of toxicants and potential associations with ASD.	Not reported
González-Alzaga et al. (2014)	3.262 Q1 (21/87, Toxicology)	20 (children)	Spanish, English, French or Portuguese	Up to 2012	PubMed, Scopus, Embase and Lilacs	10/20 cohort 9/10 cross-sectional 1/10 case–control	Original articles carried out in children and adolescents up to 16 years of age. Evaluating prenatal and/or postnatal exposure to OP pesticides. Using general intelligence tests or specific tests to assess changes in children mental and motor development or behavior. Case series studies were excluded.	Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Statement checklist.
Muñoz-Quezada et al. (2013)	3.379 Q2 (26/87, Toxicology)	27 (children)	English or Spanish	2002–2012	PubMed, Web of Science, EBSCO, SciVerse Scopus, SpringerLink, SciELO and DOAJ	12/27 cohort 14/27 cross-sectional 1/27 case study	Studies assessing exposure to OP pesticides and neurodevelopmental effects in children from birth to 18 years of age.	Studies were rated as of low, intermediate and high strength based upon study design, number of participants, exposure measurement, and neurodevelopmental measures.
Burns et al. (2013)	5.146 Q1 (8/87, Environmental Sciences)	32 (children)	English	1986–2011	MEDLINE	32/32 cohort	Epidemiologic studies reporting data on pesticide exposure during critical periods of brain development (e.g., in utero, infancy, or early childhood) and neurodevelopmental endpoints measured in infancy or early childhood. Studies ascertaining pesticide exposure by questionnaires, environmental monitoring (e.g., air, soil, dust), or biomarkers.	Not reported
Jurewicz et al. (2013)	1.126 Q3 (154/223, Environmental Sciences)	15 (children)	English	Since 2000	Pubmed, Medline and EBSCO	10/15 Cohort 5/15 Cross-sectional	Human studies. Key words referred to exposure (pregnancy, prenatal exposure, postnatal exposure, exposure to OP and OC pesticides) and outcome (neurodevelopment, psychomotor development, behavioral problems, cognitive development, mental health, school achievements, learning abilities and IQ).	Not reported
Polanska et al. (2013)	1.094 Q3 (117/162, Public, Environmental & Occupational Health)	7 (children)	English	Since 2000	Medline, PubMed and EBSCO	5/7 Cohort 2/7 Cross-sectional	Studies analyzing the association between prenatal and postnatal children's exposure to industrial chemicals and ADHD or ADHD-related symptoms. Relevant studies were also identified via a review of references cited in published studies.	Not reported
Koureas et al. (2012)	3.145 Q2 (25/85, Toxicology)	19 13/19 children 6/19 workers	English	Up to 2011	Scopus, Pubmed, Science-Direct and Google Scholar	9/19 Cohort 10/19 Cross-sectional	Measurement of pesticide compounds (OP,PYR) and their metabolites in human biological samples in association with adverse health effects	Not reported
Julvez and	1.215	8 children	English	1998–2008	PubMed and	4/8 cohort	Epidemiological studies focused on	Not reported

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Table 1 (continued)

Author (year)	Journal IF/ranking	Articles reviewed (n)	Language	Search dates (years)	Search databases	Type of study	Inclusion criteria	Methodological quality assessment
Grandjean (2009)	Q3 (115/181, Environmental Sciences)				PSYCHinfo	3/8 cross-sectional 1/8 case–control	occupational exposure to industrial chemicals and subsequent consequences on the offspring's neurodevelopment.	

ASD: Autism Spectrum Disorder; OC: organochlorine; OP: organophosphate; PYR: pyrethroids.
IF: Impact factor at the year of publication; Q1–Q4: journal ranking based on the IF distribution the journal occupies for its subject category (knowledge field) the year of publication.

adverse effect of interest and quantitatively measuring exposure to individual pesticides.

2. Methods

2.1. Search strategy

We conducted a comprehensive literature search of SRs pertaining to pesticide exposure and a number of neurological outcomes, namely neurodevelopmental abnormalities and neurodegenerative diseases (PD and AD). The search strategy was designed so as to identify SRs examining the relationship between any pesticide exposure and the aforementioned neurological disorders. Two independent reviewers searched the PubMed and the Web of Science (WoS) using different text word combinations depending on the health effect evaluated database without any language restriction to identify eligible articles. The last search was performed on 30st April 2015.

For WoS, the search included the following topics: "pesticides" AND "neurodevelopment*" AND "review"; "pesticides" AND "Parkinson*" AND "review"; and "pesticides" AND "Alzheimer*" AND "review". For PubMed, the search strategy used was the following: 1) Neurodevelopmental effects: "((("pesticides"[MeSH Terms] OR "pesticides"[All Fields]) AND neurodevelopment AND children AND review)"; 2) Parkinson's disease: "((("pesticides"[MeSH Terms] OR "pesticides"[All Fields]) AND ("parkinson disease"[MeSH Terms] OR "parkinson disease"[All Fields] OR "parkinson's disease"[All Fields] OR "parkinson"[All Fields] AND (review OR meta-analysis OR metaanalysis)))"; 3) Alzheimer's disease: ((("pesticides"[MeSH Terms] OR "pesticides"[All Fields]) AND ("Alzheimer disease"[MeSH Terms] OR "Alzheimer disease"[All Fields] OR "Alzheimer's disease"[All Fields] OR "Alzheimer"[All Fields] AND (review OR meta-analysis OR metaanalysis)))".

MeSH terms were not exploded for the outcome "neurodevelopment" because they restricted the search results and excluded SRs that met the inclusion criteria. In contrast, the search strategy "pesticides" [MeSH Terms] was exploded as it includes a wide variety of chemicals used to destroy pests of any sort (insecticides, fungicides, herbicides, rodenticides, etc.). Thus, it was not necessary to conduct a particular search for any of these pesticide groups or individual compounds. Also, two authors independently conducted the screening of studies for eligibility based on the inclusion/exclusion criteria.

2.2. Selection criteria

The articles selected for the review met the following inclusion criteria: (a) being SRs; (b) published before or during April 2015; (c) without language restrictions; (d) evaluating the association of pesticide exposure with neurodevelopmental effects in children or with PD and AD in adults. Review articles on the same topics that did not explicitly describe themselves as a SR in the title, abstract or key words but which nevertheless used a systematic approach were also selected. These included reviews meeting the following criteria: 1) having a search strategy, 2) describing information sources; and 3) summarizing results of individual studies according to some of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statements for reporting systematic reviews (Liberati et al., 2009).

2.3. Data collection and analysis

Two independent reviewers extracted information of interest from the SRs for each neurological outcome selected. Data from eligible studies that met the inclusion criteria were then collected and summarized in two tables for each outcome recapitulating the following study characteristics: (a) data on the first author and year of publication; (b) journal impact factor and journal ranking in the scientific categories listed by Thomson Reuters Journal Citation Report for the year of publication (which might be informative on the reliability of information provided in scientific articles); (c) number of original articles included in each SR; (d) languages of articles selected; (e) search dates; (f) search databases used for the review; (g) type and number of study designs included in the SR; (h) inclusion criteria and (i) type of methodological quality assessment conducted by each SR, if any. The second table collected data on: (j) how pesticide exposure was assessed (questionnaire, biomonitoring, job exposure matrices); (k) description of exposure levels (including the type of pesticide assessed and/or its concentration in biological fluids, if available); (l) major results obtained (including the effect size estimate and its uncertainty when available, the comparison level); (m) whether statistical analyses were adjusted for confounders; (n) whether results were stratified by sex/gender; (o) the size of the study population pooled from original studies; and (p) whether the study is relevant for risk assessment (based on problem formulation, whether the hazard is supported or not by the SR, how exposure and neurological outcomes were assessed in individual studies, and whether or not a meta-analysis was performed). Information provided in the tables was used to compare the SRs selected and to assess their usefulness for risk assessment.

3. Main results

Fig. 1 shows the PRISMA flow chart of SRs assessing pesticide exposure and neurodevelopmental effects. From a total of 65 articles identified in the first search, only 8 were true SRs including two of them that did not describe themselves as a SR in the text but met the criteria for a SR. Table 1 provides an overview of the main bibliometric and methodological characteristics of the selected SRs evaluating neurodevelopmental effects from exposure to persistent and non-persistent pesticides. A total of 8 SRs published between 2009 and 2014 were identified. The number of original articles included in each SR ranged from 7 to 32. Different criteria for study selection were observed in the SRs and only two of them conducted a methodological quality assessment. A relatively high number of outcomes was assessed under the broad term "neurodevelopment", as it included autism spectrum disorders (ASD), attention deficit and hyperactivity disorder (ADHD), abnormal newborn reflexes, intelligence quotient (IQ) and changes in mental and motor development (assessed by means of

Table 2
Summary of exposure assessment and major results of SRs evaluating neurodevelopmental effects from exposure to persistent and non-persistent pesticides.

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
Rossignol et al. (2014)	2/6	4/6	–	Not reported	Prenatal exposure (6 studies) Increased risk of ASD in children with increased prenatal exposure to dicofol and endosulfan (OR 6.1; 95%CI 2.4–15.3; n = 465) (1/6). Increased levels of CPF in cord plasma (N6.17 pg/g) significantly associated with increased risk of PDD at 36 months (OR 5.39; 95%CI 1.21–24.11; n = 254) (1/6). log_{10}DAP levels in maternal urine associated with increased risk of PDD at 24 months (OR 2.3; 95%CI 1.0–5.2; n = 531) (1/6). DDE levels in maternal blood during pregnancy non-significantly associated with increased risk of developing ASD (≥7 years) (1/6). Postnatal exposure (3 studies) log_{10}DAP levels in child urine associated with risk of PDD symptoms at 24 months (OR 1.7; 95%CI 1.0–2.9; n = 531) (1/3). Two children with ASD had parents directly exposed to phosphine (1/3).	Not reported	Not reported	Case control studies: 540 cases and 7050 controls. Other designs: 2317	For problem formulation and hazard identification No meta-analysis was reported
González-Alzaga, et al., 2014	5/20	15/20	–	Prenatal exposure DAP levels in maternal urine (nmol/l) 81.3–128 (median range) CPF levels in cord blood (pg/g) Exposed: N6.17; Non-exposed (≤6.17) CPF in maternal blood (pg/g) 0.36–3.17 (median range) Postnatal exposure DAP levels in child urine (nmol/l) 45.5–118.3 (median range)	Prenatal exposure (13 studies) DAP levels in maternal urine significantly associated with: a) Increase in number of abnormal reflexes in newborns (2/13). b) Decrease in MDI at 24 months (1/13). c) Increased risk of attention problems and ADHD at 5 years (1/13). DAP levels in maternal urine non-significantly associated with: a) Decrease in MDI at 12 months (only Black/Hispanic) (1/13). b) Poorer performance on PR, PS, WM and FSIQ (6–9 years) (2/13). Increased CPF levels in cord blood significantly associated with: a) Lower MDI and PDI at 36 months (1/13). b) Poorer performance on WM domain (2/13) and lower IQ (1/13) at 7 years. Maternal exposure significantly associated with: a) Lower motor function (6–8 years) (1/13). b) Decrease in visual–spatial function at 7 years (1/13). Mother working in the floriculture during pregnancy significantly associated with poorer scores on communication, motor skills and visual acuity (9–18 months) (1/13). Postnatal exposure (13 studies) DAP levels in child urine associated with: a) Significant increase in MDI at 24 months (1/13). b) Increased reaction time (4–8 years) (2/13). c) Significant risk of ADHD diagnosis (8–15 years) (1/13). No effect observed between DAP levels in child urine and motor behavior (24 months) (1/13); risk of attention problems (3.5–5 years) (1/13); performance on WISC-IV scale (1/13) and WISC-III scale (1/13) (PR, PS, VC, WM, FSIQ) (5–9 years). TCPy levels in child urine not associated with performance on BARS (4–10 years) (1/13).	Yes	3/20 articles stratified by gender (2 cohort studies and 1cross-sectional study)	Prenatal exposure: 3289 Postnatal exposure: a) Case–control study: 9 cases and 9 controls. b) Other studies: 3453	For problem formulation, hazard identification and exposure assessment No meta-analysis was reported

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Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					Significant differences in response times and latency between exposed and non-exposed children (4–6 years) (1/13). Acute intoxication by OP before age 3 associated with a significant deficit in motor control (6–12 years) (1/13). No significant differences in mental o motor development between children exposed and non-exposed to PNP (≤6 years) (1/13). Children working in agriculture performed significantly poorer on memory speed, spatial relations, attention and audio and visual memory, compared to the control group (9–15 years) (1/13).				
Muñoz-Quezada et al. (2013)	9/27	18/27	–	Not reported	Prenatal exposure (11 studies) DAP levels in maternal urine associated[a] with: a) Increased abnormal reflexes in newborns (2/11). b) Decrease in MDI at 12 (1/11) and 24 months (1/11). b) Lower IQ at 7 years (1/11). c) Poorer performance on PS domain (6–16 years) (1/11). d) Increased risk of attention problems and ADHD at 5 years (1/11) and PDD at 24 months (1/11). CPF levels in cord blood associated[a] with: a) Decrease in MDI and PDI at 36 months (1/11). b) Increase risk of attention symptoms, ADHD and PDD problems (1/11). c) Lower scores on WM and FSIQ at 7 years (1/11). Maternal exposure to pesticides during pregnancy associated[a] with decreased solving problems skills, visual acuity and fine motor skills (2–5 years) (1/11). Postnatal exposure (15 studies) Parental occupation in agriculture associated[a] with lower response speed and sustained attention (4–5 years)(1/15). PNP levels associated[a] with decreased motor skills and short term memory (≤6 years) (1/15). Proximity to crops associated[a] with: a) Decreased short term memory and visual acuity (11–16 years) (1/15). b) Poorer fine and gross skills and social individual skills (2–5 years) (1/15). Increased index of pesticide exposure associated[a] with decreased motor speed and selective attention (10–18 years) (1/15). DAP levels in child urine associated[a] with: a) Increased reaction time (6–8 years) (1/15). b) Low scores in cognitive skills and postural stability (Wisconsin Card Sorting Test) (5–8 years) (1/15). c) Increased risk of hyperactivity and ADHD (8–15 years) (1/15). d) Decrease in attention function (6–8 years) (1/15). No associations found between DAP levels and MDI (2/15); IQ (1/15); motor scores (1/15) and social scores (1/15). Previous poisoning by OPs pesticides associated[a] with decreased verbal memory and inhibitory control at 9 years (1/15). Child's occupation in agriculture associated[a] with lower IQ, decreased attention and audio and visual memory (9–18 years) (1/15).	Not reported	Not reported	Pre-and postnatal exposures: 7323	For problem formulation and hazard identification No meta-analysis was reported

Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
Burns et al. (2013)	–	32/32	–	Prenatal exposure DDE in cord blood: 0.10 ng/g ρ,ρ′-DDE in cord blood: 0.85–1.63 ng/ml ρ,ρ′-DDE in cord blood: 0.3 ng/g ρ,ρ′-DDT in cord blood: 0.05–0.17 ng/ml ρ,ρ′-DDT in maternal blood: 14.1–22 ng/g ρ,ρ′-DDE in maternal blood: 1103.7 ng/g ρ,ρ′-DDE in maternal blood: 6.3–7.9 ng/ml DDE in maternal blood: 1436.9 ng/g DDE in maternal blood: 0.6 μg/l DAP levels in maternal urine: 82–132 nmol/l TCPy in maternal urine: 3.5 μg/l cis-permethrin in maternal and cord blood: b0.1 pg/g trans-permethrin in maternal and cord blood: b0.1 pg/g CPF in cord blood: 3.17 pg/g HCB in cord blood: 0.68–1.13 ng/ml Postnatal exposure DAP levels in child urine: 45.5–92.6 nmol/l	Newborns (7 studies) Increase of abnormal reflexes associated with: a) Maternal log_{10}DAP levels: (n = 175) β = 0.23 (95%CI 0.05–0.41). No effects observed for habituation, orientation, motor performance, range of state, regulation of state and autonomic stability. b) Maternal log_{10}DEP levels: (n = 239) RR 1.49 (95%CI 1.12–1.98). No effects observed for habituation, orientation, motor performance, range of state, regulation of state and autonomic stability. c) Maternal MDA levels: (n = 242) RR 2.24 (95%CI 1.55–3.24). No effects observed for habituation, orientation, motor performance, range of state, regulation of state and autonomic stability. Inverse correlation between DDE and FTII at 12 months (n = 216; r = − 0.143; p = 0.034). Number of abnormal reflexes in newborns not significantly associated with: a) Maternal DDE levels. b) Maternal log_{10}ρ,ρ′-DDT levels. c) Maternal log_{10}ρ,ρ′-DDE levels. d) Maternal HCB levels. Children aged 6–36 months (11 studies) Maternal log_{10}DAP levels inversely associated with: a) Performance in Bayley MDI at 24 months: (n = 445) β = − 3.54 (95%CI − 6.59, − 0.49). No effect observed neither for Bayley MDI at 6 or 12 months nor for Bayley PDI at 6, 12 and 24 months. b) Performance in Bayley MDI at 12 months (only black/hispanic subject) (n = 111) log_{10}β = − 3.29 (95%CI = − 5.88, − 0.70). No effect observed for Bayley PDI. Maternal TCPy levels (N3.54 μg/l vs. ≤ 3.54 μg/l) not associated with MDI or PDI at 6, 12 or 24 months. DAP levels in child urine not associated with MDI or PDI at 6, 12 or 24 months. CPF levels in cord blood (N6.17 pg/g vs. ≤ 6.17 pg/g): a) Associated with increased risk of mental and psychomotor delay at 36 months: (n = 228) OR 2.37 (95%CI 1.08, 5.19); OR 4.52 (95%CI 1.61, 12.70), respectively. b) Inversely associated with Bayley MDI and PDI at 36 months: (n = 266) β = − 3.2 (95%CI = − 5.1, − 1.3); β = − 6.9 (95%CI − 11.1, − 2.7), respectively. MDA levels in maternal urine not associated with MDI or PDI at 6, 12 or 24 months. log_2ρ,ρ′-DDE in cord blood inversely associated with MDI and PDI at 13 months. (n = 92) β = − 3.44 (SE = 1.39; p b 0.05) and β = − 3.83 (SE = 1.46; p b 0.05), respectively. log_2 ρ,ρ′-DDE levels in maternal blood (1st trimester) inversely associated with PDI at 12 months. (n = 244) β = − 0.52 (95%CI − 0.96, − 0.075; p = 0.02). No effects observed for MDI.	Yes	2/32 stratified by gender (both were cohort studies).	Newborns: 2059 Children aged 6–36 months: 2012 Children aged 3–9 years: 1884	For problem formulation, hazard identification and exposure assessment No meta-analysis was reported

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Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					log_{10} DDT serum levels inversely associated with: a) MDI at 12 months (β = − 1.71; 95%CI − 3.21, − 0.21) and 24 months (β = − 2.12; 95%CI − 4.03, − 0.21) (n = 327). No effects observed at 6 months. b) PDI at 6 months (β = − 1.73; 95%CI − 3.36, − 0.10) and 12 months (β = − 2.33; 95%CI − 4.44, − 0.22) (n = 327). No effects observed at 24 months. HCB levels in cord blood not associated with either MDI or PDI. cis- or trans-permethrin levels in cord blood not associated with MDI or PDI at 36 months. Children aged 3 years and older (9 studies) log_{10} DAP levels (averaged over pregnancy) associated with decreased FSIQ at 7 years. (n = 297) β = − 5.6 (95%CI = − 9.0, − 2.2; p b 0.01). DAP levels in maternal urine not significantly associated with performance on WISC-IV or WPPSI-IV (PR, PS, VC, WM, FSIQ). DAP levels in child urine at 6, 12, 24, 48 and 60 months, not associated with FSIQ at 7 years. CPF levels in cord blood inversely associated with WISC-IV scores (ln-transformed) (n = 265) β = − 0.006 (95%CI = − 0.01, − 0.002). log_2 DDT levels in cord blood associated with decreased score in MSCA (General Cognitive) at 4 years: (n = 475) β = − 1.99 (SE = 0.75; p b 0.05). DDE levels in placental tissue correlated with FSIQ score (WISC-III) at 9 years: (n = 187) r = 0.163, p b 0.05. HCB levels in cord blood not associated with scores in MSCA at 4 years. Behavioural assessment (2 years and older) (7 studies) log_{10} DAP levels in child urine associated with increased risk of PDD at 24 months: (n = 373) OR 1.71 (95%CI 1.02, 2.87). No effects observed for attention problems or ADHD problems. Maternal log_{10} DAP levels associated with increased risk of attention problems and ADHD problems at 5 years: (n = 322) β (range) = 0.6 (95%CI 0.2, 1.0) to 1.3 (95%CI 0.4, 2.1). log_{10} DAP levels in child urine not associated with increased risk of attention problems or ADHD problems at 3.5 and 5 years. Maternal TCPy and MDA levels not associated with CBCL outcomes. CPF levels in cord blood significantly associated with increased risk of attention problems, ADHD problems and PDD at 36 months: (n = 228) OR (range) 5.39 (95% CI 1.21, 24.11) to 11.26 (95%CI 1.79, 70.99). ρ,ρ′-DDT levels in cord blood not associated with scores in Conner's Rating Scale for teachers. DDE levels in cord blood not associated with number of errors in CPT at 8 or 9.5 years.				

Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					HCB levels in cord blood associated with: a) Decreased score in Social Competence Scale at 4 years: (n = 377) RR 5.63 (95%CI 2.13, 14.88). b) Increased risk of ADHD symptoms at 4 years: (n = 377) RR 3.43 (95%CI 1.24, 9.51).				
Jurewicz et al. (2013)	1/15	14/15	–	Not reported	Prenatal exposure (11 studies) DAP levels in maternal urine associated[a] with increased number of abnormal reflexes in newborns. MDA levels in maternal urine NLOD associated with increased risk of abnormal reflexes (OR 2.24; 95%CI 1.55–3.24). DAP levels in maternal urine inversely associated[a] with: MDI at 24 months and an increased risk of PDD at 24 months. CPF levels in cord blood significantly associated with poorer scores on Bayley PDI and MDI at 36 months. DDE levels in maternal blood (first trimester) significantly associated with decrease in PDI at 12 months, but not in MDI. DDE levels in cord blood not associated with performance on FTII at 12 months. ρ,ρ′-DDT levels in maternal blood associated[a] with lower PDI at 6 and 12 months. ρ,ρ′-DDE levels in maternal blood associated[a] with lower PDI at 6 months. DDT levels in cord blood inversely associated with: a) MDI and PDI at 13 months[a]. b) Quality of alert responsiveness, cost of attention and other attention-associated measures (5–22 days)[a]. c) Scores in verbal and memory scale at 4 years[a]. No effect observed for HCB levels in cord blood and neurodevelopment at 12 months. Postnatal exposure (6 studies) DAP levels in child urine associated with: a) Increased risk of PDD at 24 months[a]. b) Increase in attention-related performance errors at 7 years[a]. c) Increased reaction time at 7 years[a]. Children with higher exposure to PNP showed difficulties solving tasks involving short-term memory and attention (≤6 years)[a]. Children living in agricultural areas performed significantly worse on response speed and latency compared to children living in non-agricultural areas (4–6 years).	Yes	Nor reported	Pre- and postnatal exposures: 2223	For problem formulation and hazard identification No meta-analysis was reported
Polanska et al. (2013)	7/7	–	–	Not reported	Prenatal exposure (5 studies) DAP levels in maternal urine significantly associated with: a) Risk of PDD at 24 months. b) Attention problems and ADHD at 5 years but not at 3.5 years. CPF levels in cord blood significantly associated with more attention problems and increased risk of PDD at 3 years. DDE levels in cord blood inversely and significantly associated with alertness, quality of alert responsiveness and cost of attention. Children more exposed to ρ,ρ′-DDE (N1.58 ng/g lipid) showed significant risk of ADHD (7–11 years).	Yes	Not reported	Pre- and postnatal exposures: 3483	For problem formulation and hazard identification No meta-analysis was reported

(continued on next page)

Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					Postnatal exposure (4 studies) DAP levels in child urine significantly associated with: a) Risk of PDD at 24 months. b) Attention-related performance errors at 7 years. c) Risk of being diagnosed as having ADHD (8–15 years). DAP levels in child urine not associated with CBCL attention problems (6–24 months).				
Koureas et al. (2012)	–	13/13	–	Not reported	Prenatal exposure (8 studies) DAP levels in maternal urine associated with: a) Significant risk of abnormal reflexes in newborns (2/8). b) Decreased MDI at 12 and 24 months[a] (2/8). c) Lower IQ at 7 years (2/8). d) Increased risk of attention problems (1/8). CPF levels in cord blood significantly associated with: a) Motor and mental delay (1/8). b) Attention problems and ADHD disorders (1/8). PYR levels in maternal urine not associated with performance on Bayleys Scale. Postnatal exposure (9 studies) DAP levels in child urine associated[a] with: a) Increased risk of ADHD (1/9). b) Increased reaction time (2/9). c) Poorer cognitive skills (Wisconsin Card Sorting Test) (1/9). d) Increased MDI (1/9). DAP levels in child urine not associated with: a) Cognitive scores (1/9). b) Attention problems (1/9). c) PDD (1/9). d) Increase in abnormal reflexes (1/9). PYR levels in child urine not associated with performance on Bayleys Scale (1/9). Occupational exposures (6 studies) CPF exposure not associated with central nervous system dysfunction and clinical or subclinical peripheral neuropathy (1/6). Chronic exposure to CPF affects peripheral nerve electrophysiology (significant association) (1/6). Cumulative exposure to OP (exposed sheep dippers vs. non-exposed) associated[a] with increased neurologic symptoms (2/6). TCP levels in termiticide applicators urine significantly associated with increased number of neurologic symptoms (1/6) and postural sway (1/6). OP exposure (high vs. low exposure) associated[a] with neurologic and neurobehavioral deficits (3/6).	Not reported	Not reported	Pre- and postnatal exposures: 4347	For problem formulation and hazard identification No meta-analysis was reported
Julvez and Grandjean (2009)	2	6	–	Not reported	Prenatal exposure (8 studies) OC and OP levels in maternal blood associated[a] with decreased gross and fine motor skills, and drawing skills. No effects observed for memory (1/8). DAP levels in maternal urine associated[a] with: a) Increased risk of abnormal reflexes (1/8). b) Increased risk of PDD (1/8). c) Decreased MDI (1/8). Parents working in agriculture associated[a] with lower visuospatial performance.	Yes	Not reported	Case–control studies: 52 cases and 70 controls. Other studies: 1633	For problem formulation and hazard identification No meta-analysis was reported

Table 2 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					Mother working in floriculture industry during pregnancy positively associated[a] with communication skills, problem solving and with decreased visual acuity (2/8). DDT and DDE levels in maternal blood associated[a] with lower MDI and PDI (1/8). DDT and DDE levels in maternal blood not associated with performance on BNBA in newborns (1/8). Postnatal exposure (3 studies) DAP levels in child urine associated[a] with: a) Increased MDI (1/3). b) Increased reaction time (1/3). Mother currently working in floriculture industry associated with better communication and problem solving skills (1/3).				

ADHD: Attention deficit hyperactivity disorder; B: biomarkers; BARS: Behavioural Assessment and Research System; BNBAS: Brazelton neonatal behavioral assessment scale; CBCL: Child Behaviour Checklist; CPF: chlorpyrifos; CPT: Continuous Performance Test; CTSB: copying test of the Stanford-Binet; DAP: dialkyl phosphates; FSIQ: Full Scale Intelligence Quotient; FTII: Fagan Test of Infant Intelligence; FTT: finger tapping test; GDS: Gesell Developmental Schedules; JEM: job-exposure matrix; LOD: Limit of detection; MDA: Malathion Dicarboxylic acids; MDI: mental developmental index; MSCA: McCarthy Scale of children's abilities; OC: organochlorine; OP: organophosphate; PDD: pervasive development disorder; PDI: psychomotor developmental index; PR: perceptual reasoning; PS: processing speed; PYR: pyrethroids; Q: questionnaire; VC: verbal comprehension; WISC-IV: Wechsler Intelligence Scale for Children (IV); WM: working memory; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence.

[a] Significance level of the association not indicated in the review.

different neuropsychological tests). Although some SRs assessed not only pesticides but also other chemicals (e.g., industrial chemicals), the latter were not considered for the purpose of this review. Most SRs included cohort studies and to a lesser extent cross-sectional and case–control studies.

Table 2 summarized data on exposure assessment and the main results in relation to neurodevelopmental effects associated with persistent and non-persistent pesticide exposure. Biomonitoring was the most common way used to assess exposure by quantifying pesticide metabolites in urine from pregnant women and children, or parental compounds in cord blood. All SRs selected distinguished between prenatal and postnatal exposure to pesticides, with only one study including occupational exposure as well (Koureas et al., 2012). Five SRs reported on confounding variables in the original studies and 2 SRs reported data on gender/sex stratification. The major pesticides studied were as follows: dialkylphosphates (DAPs, common metabolites of OPs) in 8 studies, chlorpyrifos in 6 studies, trichloropyridinol (TCPy, chlorpyrifos metabolite) in 3 studies, malathion dicarboxylic acid (MDA) in 3 studies, organochlorines (DDT, DDE, dicofol, endosulfan, HCB) in 5 studies and pyrethroids in 2 studies. While 7 out of the 8 SRs included studies evaluating exposure by means of biomarkers, only 2 SRs reported ranges for pesticide concentrations. Qualitative data on exposure was also reported, e.g. children living/working in agriculture (3 SRs), mother working during pregnancy (2 SRs), living near crops (1 SR), index of pesticide exposure (1 SR), parental exposure to pentanitrophenol (3 SRs), parental exposure to phosphine (1 SR) and sequels of acute intoxication (2 SRs). No meta-analysis was reported by any of the 8 SRs assessed.

Fig. 2 shows the PRISMA flow chart of SR articles assessing pesticide exposure and Parkinson's disease (PD). From a total of 304 articles identified in the first search, only 10 were true SRs including four that did not mention this explicitly in the text but met the criteria for a SR. Table 3 provides an overview of the main bibliometric and methodological characteristics of the selected SRs. The 10 SRs identified were published between 2000 and 2013 and although the number of original articles included in each SR ranged from 12 to 173, those dealing specifically with pesticides and PD ranged from 2 to 89. Three studies assessed the association between exposure to environmental risk factors (including pesticides) and PD. One SR covered the association between exposure to glyphosate and a number of non-cancer disorders, including PD. Criteria for study selection differed across SRs, but most of them considered the type of study design, characterization of pesticide exposure, definition of PD and language of publication. Only one SR conducted a methodological quality assessment. Most reviews included case–control studies, except one that only included cohort studies.

Table 4 summarizes major data on exposure assessment and main results in relation to the association between exposure to pesticides and PD. In seven SRs exposure was assessed by means of questionnaire, whereas three included studies assessing exposure by using job exposure matrices (JOM). Only one SR included original articles assessing exposure by biomonitoring techniques. Sometimes, proxies of exposure were used (e.g., occupation, rural living, well water drinking) and occasionally exposure was related to the length of time working as farmer or handling pesticides. However, 3 SRs did not mention how pesticide exposure was assessed in the original articles reviewed, with one of them defining exposure as a broad exposure category. Seven out of the 10 SRs carried out a quantitative meta-analysis, but the statistical estimates for the overall effect size were based on type of exposure (broad definition, occupational exposure, ...) and broad groups of pesticides (organochlorine, rodenticides, paraquat, ...). Five SRs reported analysis for confounders and 4 SRs included stratification by sex/gender. Only 5 SRs reported a combined estimate for the size effect (overall OR/RR) ranging from 1.27 to 1.94, which was statistically significant in all cases. Six SRs provided quantitative data from cohort studies, with 4 of them showing significant associations with PD. The remaining two SRs which found non-significant associations were performed by the same authors and reported in the years 2000 and 2001, so a large number of original studies were repeated in both studies. The combined effect size of the original studies was reported by 6 SRs, and all of them found statistically significant associations of pesticide exposure and PD, with OR/RR ranging between 1.28 and 1.94. Nevertheless, there were also original studies that found non-significant associations.

Fig. 3 shows the PRISMA flow chart of SRs articles assessing pesticide exposure and AD. From a total of 108 articles identified in the first search, only 2 were true SRs, although one of them did not mention this explicitly in the text but met the criteria for a SR. Table 5 provides an overview of the main bibliometric and methodological characteristics of the selected SRs evaluating AD and exposure to pesticides. The

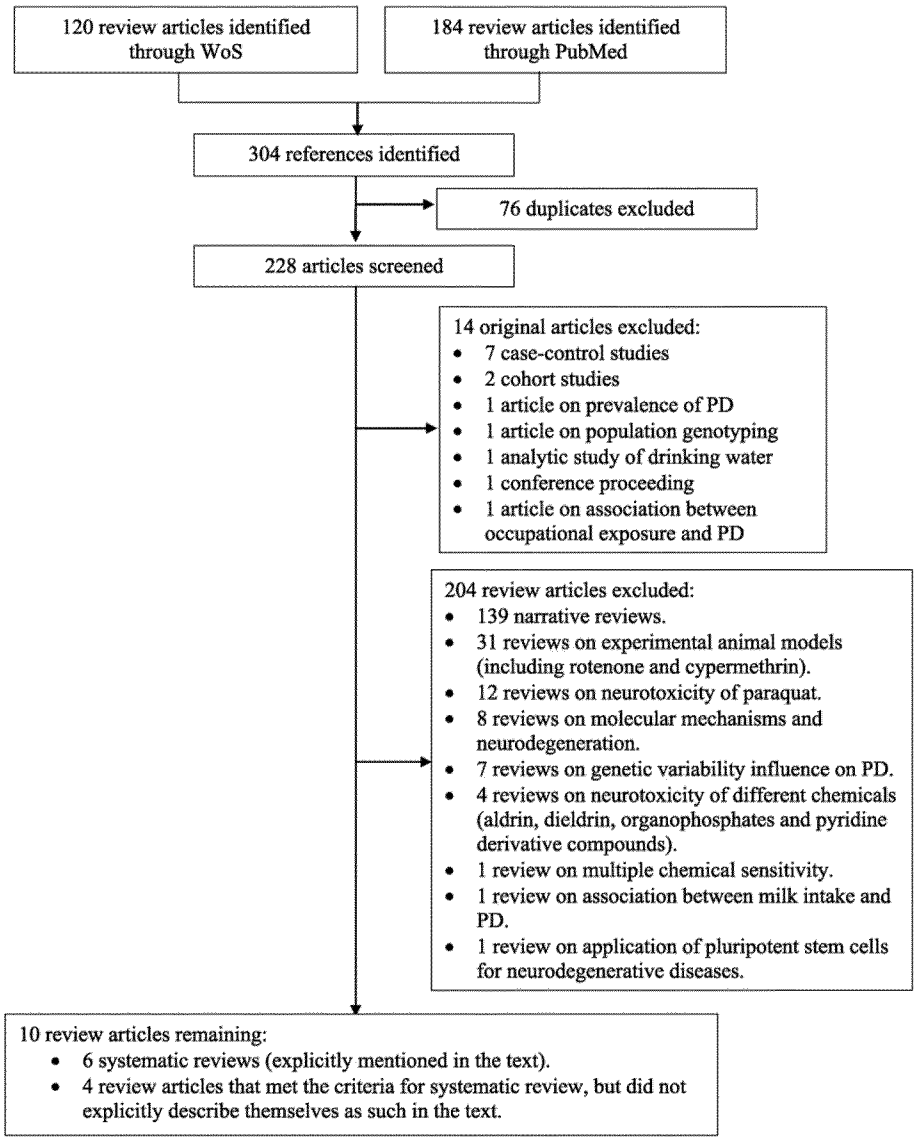

Fig. 2. PRISMA flow chart of review articles assessing pesticide exposure and Parkinson's disease (PD).

two reviews identified were published in 2007 and included 41 and 24 original studies, of which 2 and 6, respectively, specifically addressed AD. Criteria for study selection differed among the two SRs. Both of them included case–control and cohort studies, and conducted a methodological quality assessment.

Table 6 summarizes data on exposure assessment and the main results in relation to the association between exposure to pesticides and AD. Neither of the two SRs included quantitative data on pesticide exposure, and one of them did not report any data on exposure. Of the 8 original articles included in both SRs, only 2 found significant associations with AD, with OR of 2.39 and 4.35.

4. Discussion

This study has critically appraised all the SRs published to April 2015 on the association between pesticide exposure and major neurological outcomes, in particular neurodevelopment impairment and the two main neurodegenerative disorders, PD and AD. For a better understanding of the data collected from the SRs studied, the information extracted was gathered in two tables for each outcome. This is a useful way to quickly identify all relevant points reported in the SRs and to make a proper comparison of results across studies. This approach has been especially useful in the evaluation of neurodevelopmental studies, as most of them have assessed the effects associated with various pesticides, at different ages and using different tools, thus leading to a wide range of results that can be better summarized in a specific table. When appropriate, it is recommended to extract results from the original studies indicating both the age range and the range of exposure to which the effect was observed.

4.1. Neurodevelopmental disorders

Different considerations can be made on this outcome depending on the type of pesticides assessed. In the case of OPs, certain uniformity of results has been found across birth cohorts evaluating exposure to such pesticides. Overall, results suggest that prenatal exposure to OPs (assessed by biomonitoring of urinary levels of DAPs or chlorpyrifos concentration in cord blood) is linked to mental or psychomotor development as well as to children's behavior (attention problems, pervasive developmental disorder — PDD or Attention Deficit and Hyperactivity Disorder — ADHD) in both preschool and school children. In contrast, postnatal exposure to OP failed to show a clear effect across cohort studies, making it difficult to draw sound conclusions. Although some cross-sectional studies have shown adverse effects on specific functions, such

Table 3
Bibliometric and methodological features of SRs evaluating Parkinson's disease (PD) from exposure to pesticides.

Author (year)	Journal IF/rank	Articles reviewed (n)	Language	Search dates (years)	Search databases	Type of study	Inclusion criteria	Methodological quality assessment
Allen and Levy (2013)	6.414 (Q1, 6/87, toxicology)	29/49 explored the association between PD and overall pesticides exposure (adjusted effect sizes). 20/49 explored the association between PD and occupational pesticides exposure (adjusted effect sizes)	English	1947–2010 (earliest relevant study that passed the inclusion criteria was published in 1989 and latest was published in 2010)	EMBASE, MEDLINE, CAB Abstract	45/49 case control and 4/49 prospective cohort studies (28/49 case–control and 1/49 prospective cohort study on overall pesticide exposure, 17/49 case–control and 3/49 prospective cohort studies on occupational pesticide exposure)	1) Cohort, case–control or cross-sectional study design 2) studies which addressed the role of pesticides (or functional groups) in an aspect of PD (effect size, relative risk, standardized mortality ratio, standardized incidence rate ratio or standardized hospitalization ratio) with confidence interval or any information to derive it 3) studies not relying on biological monitoring data 4) original reports 5) written in English	Not reported
Pezzoli and Cereda (2013)	8.303 (Q1, 8/194 Clinical Neurology)	89/104 provided risk and precision estimates relating PD to pesticide or solvent exposure or to proxies of exposure (occupation, rural living, well water drinking)	English	1975–2011 (earliest relevant study that passed the inclusion criteria was published in 1986 and latest was published in 2011)	PUBMED, EMBASE, CINAHL	6/89 prospective cohort 83/89 case–control studies	1) Prospective cohort and case–control studies in English language 2) Studies not addressing fetal or early-life exposure 3) Studies not using mortality data for case identification of ascertainment of PD 4) To report at least one risk value relating exposure to organic pollutants (pesticides, herbicides, insecticides, fungicides, rodenticides, solvents) or proxies of exposure (occupation, rural living, well water drinking) to PD or enough data to calculate them	Yes (Newcastle-Ottawa Scale, NOS). Three parameters of quality: selection, comparability and exposure (case–control studies) or outcome (cohort studies)
Freire and Koifman (2012)	2.652 (Q2, 33/85, Toxicology)	36/50 articles assessed overall exposure to pesticides in occupational or environmental settings and PD 20/50 articles assessed exposure to specific groups of pesticides or individual pesticide compounds.	English, Spanish or Portuguese	2000–2011 (earliest relevant study that passed the inclusion criteria was published in 2000 and latest was published in 2011)	MEDLINE, SCIELO	44/56 case control studies (25/44 case control studies assessed overall exposure and 19/44 assessed exposure to specific pesticides) 9/56 prospective cohort studies (8/9 assessed overall exposure and 1/9 assessed exposure to specific pesticides) 1/56 cross-sectional study (overall exposure) 2/59 ecological, studies (overall exposure)	Epidemiological studies directly addressing environmental or occupational exposure to any type of pesticide, group of pesticides or pesticide-exposure related factors (e.g. occupation in agriculture, well-water drinking) and its association with the risk of developing PD or Parkinsonism symptoms	No
Noyce et al. (2012)	11.193 (Q1, 9/252 Neurosciences)	38/173 (173 articles evaluated the association between diagnosis of PD and risk factors or	English	1966–2011 (earliest relevant study that passed the inclusion criteria was	MedLine, PubMed	36/38 case–control studies 2/38 cohort studies	1) Assessed at least 1 risk factor or early non-motor symptom preceding a subsequent diagnosis	No

(continued on next page)

Table 3 (continued)

Author (year)	Journal IF/rank	Articles reviewed (n)	Language	Search dates (years)	Search databases	Type of study	Inclusion criteria	Methodological quality assessment
		early symptoms amenable to population-based screening, of which 38 explored relationship of PD with pesticide exposure)		published in 1989 and latest was published in 2010)			of PD 2) reported original data on relative risks or odds ratios from cohorts or case–control studies 3) reported data that could be easily obtained in a primary care environment (factors that could be determined through questionnaires or widely available blood tests)	
Van der Mark et al. (2012)	7.260 (Q1, 4/210, Environmental Sciences)	46 articles analyzed the association of pesticide use with PD	English, French, German or Dutch	1950–2010 (earliest relevant study that passed the inclusion criteria was published in 1989 and latest was published in 2010)	Embase, Medline	39/46 case–control studies 4/46 prospective cohort studies 3/46 cross-sectional studies	Cohort, case–control and cross-sectional studies that specifically investigated PD or parkinsonism	No
Van Maele-Fabry et al. (2012)	6.248 (Q1, 6/210, Environmental Sciences)	12 articles quantitatively estimated the association between occupational exposure to pesticides and PD	English	1966–2011 (earliest relevant study that passed the inclusion criteria was published in 1985 and latest was published in 2011)	Medline	12/12 Cohort studies	1) Publications referred to workers occupationally exposed to pesticides (farmers, pesticide applicators, workers-manufacture of pesticides, horticulturists, greenhouse workers, gardeners…) 2) outcome included: Parkinsonian disorders or associated diseases (PD, Parkinsonism) 3) publications presenting original data from a cohort design	No
Mink et al. (2011)	2.427 (Q2, 40/83, Toxicology)	2/24 (24 articles analyzed the association of glyphosate exposure with non-cancer health outcomes. Two out of 24 explored relationship of PD with glyphosate exposure)	English	Not indicated (studies on PD and glyphosate exposure published in 1991 and 2007)	PubMed, Biosis, EMBASE, Medline, Pascal and SciSearch	1/2 cohort 1/2 case–control	a) Published in a peer-reviewed journal b) English language c) Analytic epidemiologic studies (cohort, case–control, cross-sectional) evaluating the association between glyphosate (and a non-cancer outcome (s)	No
Brown et al. (2006)	5.861 (Q1, 1/144, Environmental Sciences)	38 case–control studies analyzed the association between pesticide exposure and PD	English or French	1983–2005 (earliest relevant study that passed the inclusion criteria was published in 1989 and latest was published in 2005)	Embase and MedLine	38/38 case–control	1) Original reports 2) Directly addressed the role of a pesticide or pesticides in an aspect of PD or parkinsonism 3) English or French language 4) Published from 1983 onward	No
Priyadarshi et al. (2001)	1.607 (Q1, 22/129 Environmental Sciences)	14/22 articles examined the association between PD and exposure to pesticides (8/22 articles examined the association with environmental factors other than pesticides).	English	As of January 2000 (earliest relevant study that passed the inclusion criteria was published in 1989 and latest was published in 1998)	Medline and PubMed	14/14 case–control studies	1) English language 2) Include pesticide exposure as a risk factor 3) Not duplicated studies with same cohort 4) Sufficient published data for determining an estimator of relative risk or a confidence interval	No

Table 3 (continued)

Author (year)	Journal IF/rank	Articles reviewed (n)	Language	Search dates (years)	Search databases	Type of study	Inclusion criteria	Methodological quality assessment
							5) Disease specifically designated as PD	
Priyadarshi et al. (2000)	1.740 (Q2, 21/77 Toxicology)	19 articles analyzed the association between pesticides exposure and PD	English	As of August 1999 (earliest relevant study that passed the inclusion criteria was published in 1989 and latest was published in 1999)	The Medical Abstract database	19/19 case–control studies	1) English language 2) Include pesticide exposure as a risk factor 3) Not duplicated studies with same cohort 4) Sufficient published data for determining an estimator of relative risk or a confidence interval 5) Disease specifically designated as PD	No

PD: Parkinson's disease; IF: Impact factor at the year of publication; Q1–Q4: journal ranking based on the IF distribution the journal occupies for its subject category (knowledge field) the year of publication.

as reaction time, speed of response or attention, the evidence available so far is limited regarding the relationship between exposure to OPs in early life and behavioral or developmental disorders in children.

As for the neurotoxic effects associated with exposure to some organochlorines, some birth cohorts found associations of levels of DDT, DDE and HCB in maternal blood samples during the pregnancy, or in cord blood at the time of delivery, with cognitive and motor function impairment. However, these associations varied with the age of children and with the neuropsychological tests used, making it difficult to draw firm conclusions.

In regards to autism spectrum disorders (ASD) and other behavioral disorders, the SRs analyzed supported a possible relationship with pre- or postnatal exposure to pesticides. However, the information available so far is not enough to draw firm conclusions because of the limited number of studies and methodological limitations related to study design (sample size of the studies, methods used to diagnose the disorder, exposure assessment, etc.).

The appraisal of SRs on neurodevelopment identified differences across studies as some of them only indicated whether an association was found between exposure and outcome (either as text or with up or down arrows in data extraction tables), without specifying if the association was statistically significant or not and without giving numerical measures on the magnitude of the association (OR or β coefficients). Likewise, some SRs failed to specify the age ranges at which the effects were observed and this is of utmost importance as most original studies assessed the effects at different ages to identify critical neurodevelopmental stages. These differences make it difficult to compare results, as uncertainty may arise in relation to the observed effect depending on the SR being assessed. Therefore, it would be useful to incorporate the significance level of any association observed, as well as whether the effect has been observed in the study population as a whole or in a particular subgroup (e.g., by age, race, or sex).

4.2. Neurodegenerative diseases

The first meta-analysis on the association between pesticide exposure and the risk of PD was conducted 15 years ago by Priyadarshi et al. (2000). Further SRs and meta-analyses conducted since then have lent support to this association. The vast majority of studies on PD are case–control in design, with the number of prospective cohort studies being much smaller. A small number of cross-sectional studies were also included in some SRs and one meta-analysis included two ecological studies. While almost all studies found a positive association between exposure to pesticides and PD, the association was not always statistically significant. A small number of studies found a negative association, however none of them reached statistical significance. The overall synthesis of studies included in the meta-analyses indicates that PD is significantly associated with pesticide exposure.

However, the association of PD with pesticide groups is less consistent. Some meta-analyses found a significant association with exposure to herbicides and insecticides (Allen and Levy, 2013; Brown et al., 2006; van der Mark et al., 2012), in line with experimental data. In contrast, the meta-analysis performed by Pezzoli and Cereda (2013) found a significant association with pesticides (broad term) and herbicides, but not with insecticides. Other meta-analyses did not find significant associations with exposure to herbicides (Mink et al., 2011) or fungicides (Allen and Levy, 2013; Pezzoli and Cereda, 2013; van der Mark et al., 2012; van Maele-Fabry et al., 2012). The SR of Freire and Koifman (2012) identified inconsistent data in the original studies reviewed regarding the association between PD and exposure to functional categories of pesticides (such as herbicides, insecticides, etc.) or chemical classes of pesticides (e.g., organophosphates or organochlorines). Thus, no conclusion can be drawn as to specific pesticide compounds and PD.

The analysis by individual pesticides showed a statistically significant association for organochlorines and paraquat, but not for organophosphates, parathion, malathion, diazinon DDT, carbamates, maneb, and pyrethroids. Most of the studies included in the meta-analysis conducted by Allen and Levy (2013) were case–control, with only a few being cohort studies. The meta-analysis conducted by Pezzoli and Cereda (2013) provided inconclusive evidence because the overall effects of pesticide exposure in cohort studies failed to be significantly associated with PD, whereas the results of case–control studies showed significant associations. Conversely, an earlier meta-analysis (Noyce et al., 2012) obtained similar values for the magnitude of association between PD and pesticide exposure irrespective of the study design (case–control or cohort studies).

Taken together, the overall appraisal of these results suggest that there is sufficient evidence to conclude an association between pesticide exposure (broad definition) and PD, but not enough to support a causal relationship with specific pesticide classes or compounds. More studies are needed to identify individual pesticides that might be associated with PD, in particular with prospective cohort design because of limitations of case–control studies, and to assess the effect of exposure to individual pesticides with a short half-life. Appropriate data on dose–response are also required; however, this may be difficult to achieve because of the long latency period of PD.

The main differences identified in the SRs on PD and exposure to pesticides are the following: a) not all SRs show an overall OR/RR estimate from the original studies selected for the review; b) not all SRs

Table4
Summary of exposureassessmentand major results of SRs evaluatingParkinson'sdisease (PD) from exposure to pesticides.

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
Allen and Levy (2013)	49/49	–	–	Pesticide exposure was categorized in the studies included as: overall exposure, occupational exposure, home exposure, exposure to different functional groups (herbicides, insecticides, fungicides, rodenticides) for both overall and occupational exposure and any exposure to specific chemical groups/agents	13/29 articles showed significant associations between PD risk and overall pesticide exposure, with OR ranging from 1.60 (95%CI 1.00–2.40) to 7.00 (95%CI 1.61–63.46). 16/29 articles did not show significant associations. The summary adjusted effect size from the 29 articles (fixed effects model) was 1.42 (95%CI 1.32–1.52). 12/20 articles showed significant associations between PD risk and occupational pesticide exposure whereas 8/20 articles did not find significant associations. The summary adjusted effect size from the 20 articles (fixed effects model) was 1.49 (95%CI 1.34–1.66). The summary adjusted effect size from the 6 articles looking at associations between PD and home pesticide exposure was 1.34 (95%CI 1.09–1.65). The summary effect size from the case–control studies exploring associations between PD and exposure to groups of pesticides (fixed effects model) was 1.27 (95%CI 1.11–1.45) for overall exposure to herbicides; 1.49 (95%CI 1.08–2.05) for occupational exposure to herbicides; 1.30 (95%CI 1.14–1.47) for overall exposure to insecticides and 1.34 (95%CI 1.00–1.78) for occupational exposure to insecticides. No significant associations were found for overall and occupational use of fungicides and for overall exposure to rodenticides. No studies addressing the relationship between PD and occupational rodenticide exposure were identified. The summary adjusted effect sizes were statistically significant (fixed effects model) for organochlorine 1.48 (95%CI 1.04–2.09) and paraquat 1.82 (95%CI 1.48–2.23). Non-statistically significant associations were found for organophosphates, DDT, carbamates, maneb, parathion, malathion, diazinon and pyretroids.	21/49 articles adjusted for confounding variables	3/49 studies (2 case control and 1 prospective cohort studies) stratified by sex/gender	Not available (missing data in some individual studies)	For problem formulation and hazard identification Meta-analysis was carried out
Pezzoli and Cereda (2013)	89/89	–	–	Pesticide exposure was categorized as any kind of exposure, occupational or home-based/environmental exposure	4/6 prospective cohort studies showed significant association between PD risk and exposure to pesticides or farming as proxies of exposure. Significant	6/6 prospective cohort studies were adjusted for	3/6 prospective cohort studies 3/89 case–control studies	14,446 cases and 104,918 controls	For problem formulation and hazard identification

Table 4 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					associations were found between PD and: a) men exposed to pesticides RR 5.63 (95%CI 1.47–21.58), b) have been farmer: RR 1.8 (95%CI 1.2–2.6) for men and RR 1.9 (95%CI 1.0–3.8) for women. c) N397 days of mixing or applying pesticides: RR 2.3 (95%CI 1.2–4.5). d) men working in agriculture and horticulture RR 1.34 (95% CI 1.09–1.62). 2/6 prospective cohort studies did not find significant associations between PD and exposure to pesticides. 48/89 case–control studies found significant associations between PD risk and exposure to any type of pesticide or proxies of exposure. OR ranged from 1.39 (95%CI 1.02–1.89) to 17.1 (95%CI 4.97–58.8). 41/89 case–control studies did not find statistically significant associations between PD risk and any kind of pesticide exposure.	confounding variables 66/89 case–control studies were adjusted for confounding variables			Meta-analysis was carried-out
Freire and Koifman, (2012)	48/56	2/56	6/56	Pesticide exposure was categorized as overall pesticide exposure (residence, water supply, occupational exposure) and exposure to specific pesticides or groups of pesticides (biomarkers, occupational and residential exposure to insecticides, herbicides, fungicides).	48/56 studies reported a significant association between overall or specific pesticide exposure and PD: 40/44 case control studies reported significant ORs, ranging from 1.10 (95%CI 1.00–1.22) for occupational pesticide spraying N1 year, to OR = 10.92 (95%CI 1.77–67.5) for history of well water drinking and young PD patients. 4/44 case control studies reported non-significant associations between overall or specific exposure to pesticides and PD. 6/9 prospective cohort studies reported significant associations, with RR ranging from 1.7 (95%CI 1.2–2.3) for exposure to pesticides or herbicides, to 5.63 (95%CI 1.47–21.58) for overall cumulative occupational exposure in men. 3/9 prospective cohort studies reported non-significant associations between overall or specific exposure to pesticides and PD. 1/1 cross-sectional study found a non-significant association between PD risk and farming. 2/2 ecological studies reported significant associations	48/56 studies adjusted for confounding variables 38/44 case control studies adjusted for confounding variables 7/9 prospective cohort studies adjusted for confounding variables 1/1 cross-sectional and 2/2 ecological studies adjusted for confounding variables.	11/56 stratified results by gender (9/44 case control, 1/9 prospective cohort and 1/1 cross-sectional studies).	Not reported	For problem formulation and hazard identification No meta-analysis was reported

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Table 4 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					between exposure to insecticides and PD, with OR of 1.21 (95%CI 1.08–1.36) and 1.49 (95%CI 1.31–1.72) for moderate pesticide use. 8/56 studies reported non-significant associations.				
Noyce et al. (2012)	38/38 (37/38 inter-view and 1/38 medical record review)	–	–	Broad pesticide exposure definition (ever vs. never exposed)	18/36 case–control studies reported significant associations between pesticide exposure and PD with OR ranging from 1.60 (95%CI 1.00–2.40) to 17.12 (95%CI 4.97–58.84). 18/36 case–control studies reported non-significant associations. Subtotal case control studies: OR 1.77 (95%CI 1.48–2.12) 1/2 prospective cohort studies reported a significant association between pesticide exposure and PD, RR 1.70 (95% CI 1.20–2.30) 1/2 prospective cohort studies reported a non-significant but marginal association: RR 2.70 (95%CI 0.98–7.43) Subtotal prospective cohort studies RR 1.78 (95%CI 1.30–2.42) Overall RR 1.78 (95%CI 1.50–2.10)	Not reported	Not reported	6415 cases and 216,053 controls	For problem formulation and hazard identification Meta-analysis was carried out
Van der Mark et al. (2012)	43/46	–	3/46	Broad pesticide exposure definition (ever vs. never exposed)	PD relative risk for any pesticide exposure was based on studies of occupational and/or non-occupational exposures and studies of only occupational exposures. The summary risk ratios (sRRs) were similar in both cases: 1.69 (95%CI 1.38–20.6) and 1.52 (95%CI 1.23–1.89). Overall sRR 1.62 (95%CI 1.40–1.88). Meta-analysis was carried out for exposure to herbicides, insecticides and fungicides. Significant associations were reported only for exposure to herbicides, overall sRR 1.40 (95%CI 1.08–1.81) and insecticides, overall sRR 1.50 (95%CI 1.07–2.11).	26/46 adjusted for confounding variables	Not reported	8304 cases and 296,149 controls.	For problem formulation and hazard identification Meta-analysis was carried out
Van Maele-Fabry et al. (2012)	11/12	–	1/12	Exposure assessment was self-reported by questionnaire including items on jobs (employment classification, duration of employment in years, area farming in acres…) or exposure based on a JEM	5/12 cohort studies reported significant associations between occupational pesticide exposure and PD: RR 1.32 (95%CI 1.11–1.56) RR 1.90 (95%CI 1.00–3.50) RR 6.63 (95%CI 1.47–21.58) RR 1.70 (95%CI 1.20–2.30) RR 5.60 (95%CI 1.18–13.00) 7/12 cohort studies reported non-significant associations. Overall meta-rate ratio calculated for all studies was 1.28 (95%CI 1.03–1.59).	10/12 adjusted for confounding variables.	6/12 reported gender/sex stratification	Not reported	For problem formulation and hazard identification Meta-analysis was carried out

Table 4 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
Mink et al. (2011)	2/2	–	–	1/2 Ever use vs. never use of glyphosate. 1/2 occupational pesticide exposure in males	2/2 studies reported non-significant associations.	Not reported	Not reported	Not reported	For problem formulation and hazard identification No meta-analysis was reported.
Brown et al. (2006)	38/38	–	–	31/38 presented results for exposure to pesticides as an exposure category	12/31 reported significant associations between pesticide exposure and PD, with ORs ranging from 1.6 (95%CI 1.0–2.4) to 7.0 (95%CI 1.61–63.46) 19/31 reported non-significant associations. Effect of exposure to specific pesticide groups: 6/6 studies reported non-significant associations between exposure to fungicides and PD. 6/15 studies reported significant associations between exposure to herbicides and PD, with ORs ranging from 1.90 (95%CI 1.05–3.40) to 4.10 (95%CI 1.37–12.24). 9/15 studies reported non-significant associations. 6/12 studies reported significant associations between exposure to insecticides and PD, with ORs ranging from 1.77 (95%CI 1.28–2.43) to 4.52 (95%CI 1.83–11.20). 6/12 studies reported non-significant associations. 2/6 studies reported significant associations between exposure to organochlorines and PD, with ORs ranging from 2.31 (95%CI 1.57–3.40) to 5.00 (95% CI 1.22–20.50). 4/6 studies reported non-significant associations.	Not reported	Not reported	Not reported	For problem formulation and hazard identification No meta-analysis was reported.
Priyadarshi et al. (2001)	–	–	–	Not reported	5/14 case–control studies reported significant associations between pesticide exposure and PD: OR 7.0 (95%CI 5.8–8.5) OR 3.32 (95%CI 1.59–6.94) OR 4.10 (95%CI 1.37–12.24) OR 3.6 (95%CI 1.0–12.9) OR = 3.22 (95%CI 2.51–4.12) 9/14 cohort studies reported non-significant associations. The combined OR for pesticide exposure was 1.85 (95%CI 1.31–2.60).	Not reported	Not reported	2439 cases and 4204 controls	For problem formulation and hazard identification Meta-analysis was carried out
Priyadarshi et al. (2000)	–	–	–	Not reported	8/19 studies were case–control in design and reported significant associations between pesticide exposure and PD: OR 3.42 (95%CI 1.27–7.32) OR 3.6 (95%CI 1.0–12.9) OR 3.22 (95%CI 2.51–4.12) OR 2.25 (95%CI 1.27–3.99)	Not reported	Not reported	2401 cases and 6070 controls	For problem formulation and hazard identification Meta-analysis was carried out

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Table 4 (continued)

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
					OR 7.0 (95%CI 5.8–8.5) OR 2.06 95%CI (1.62–2.62) OR 3.32 (95%CI 1.59–6.94) OR 4.10 (95%CI 1.37–12.24) 11/19 studies were cohort in design and did not report significant associations. The combined OR for all studies was 1.94 (95%CI 1.49–2.53)				

have conducted analysis by pesticides groups; c) while the associations found for PD are significant for overall exposure to pesticides (broad definition) or for exposure to specific groups of pesticides, the magnitude of the association varies. Thus, Allen and Levy (2013) found lower magnitudes of association than van der Mark et al. (2012) for overall and occupational exposure to pesticides (broad definition) and for exposure to herbicides or insecticides. Differences likely lie in the distinct features of studies included in the meta-analyses.

According to data from epidemiological studies, pesticides are among the environmental factors that have been associated with the development of AD. A SR on the occupational risk factors and risk of AD (Santibáñez et al., 2007) assessed epidemiological studies published until 2003. Eleven studies addressed an association with exposure to organic solvents, 7 with electromagnetic fields, 6 with pesticides, 6 with lead and 3 with aluminum. The greatest evidence of the association was found for occupational exposure to pesticides. Gender stratification showed a stronger association for men, very likely because their work activities involved greater occupational exposure to these compounds. The SR of Sanborn et al. (2007) on the association between pesticide exposure and various non-cancer outcomes found evidence of an association between pesticide exposure and AD. However, of the two original studies included in the review, only one found a significant association and only for men.

The description of exposure to pesticides was in general poor for PD and AD and this limitation is difficult to overcome as these are chronic diseases with long latency periods and it is challenging to assess

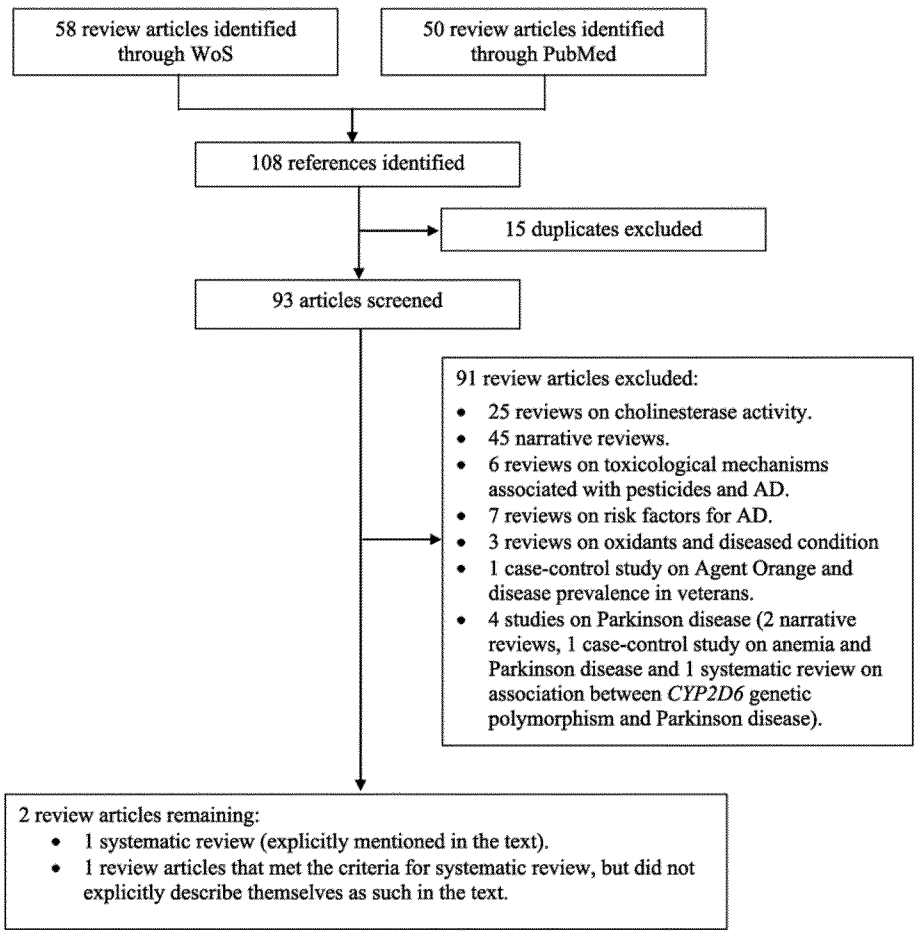

Fig. 3. PRISMA flow chart of review articles assessing pesticide exposure and Alzheimer's disease (AD).

Table 5
Bibliometric and methodological features of SRs evaluating Alzheimer's disease (AD) from exposure to pesticides.

Author (year)	Journal IF/rank	Articles reviewed (n)	Language	Search dates (years)	Search databases	Types of study	Inclusion criteria	Methodological quality assessment
Sanborn et al. (2007)	0.933 (Q3, Medicine, General & Internal)	2/41 (124 articles in total of which 41 explored relationship of neurotoxicity with pesticide exposure; 2 out of these 41 articles studied AD)	2/2 English	2001–2003	preMedline, MEDLINE y LILACS	1/2 prospective cohort 1/2 case–control	Peer reviewed studies, being a study related to pesticide exposure and being published between 1992 and 2003	Yes (with a mean quality score of 4.88 out of 7). Studies scoring b4 on a 7-point global methodological quality scale were excluded)
Santibáñez et al. (2007)	2.817 (Q1, Public, Environmental & Occupational Health)	6/24 (24 articles in total of which 6 explored relationship of AD with pesticides, 11 with solvents, 7 with electromagnetic fields, 6 with lead and 3 with aluminum)	6/6 English	1985–2003	Pubmed, and Toxline	2/6 prospective cohorts 4/6 case–control	Epidemiological studies with individualized data in which it was possible to calculate measurements of relative risk for AD (specific clinic diagnosis of AD) among exposed individuals at least once (occupational exposure only) and those never exposed.	Quality evaluation of the studies was performed using a specially designed questionnaire. The median Global Quality Index was 36.6% (range 19.5–62.9%).

AD: Alzheimer's disease; IF: Impact factor at the year of publication; Q1-Q4: journal ranking based on the IF distribution the journal occupies for its subject category (knowledge field) the year of publication.

exposure retrospectively and adequately for long periods of time. Besides, pesticides currently used are different from those used in the past 3–4 decades as organochlorines were banned in the seventies and many OPs have been restricted or banned in developed countries since the year 2000. Thus, even an appropriate characterization of pesticide exposure at present is expected to have an impact (if any) on the risk of these neurodegenerative diseases within some decades. However, this long latency period may be reduced if accurate and validated surrogate markers of PD and AD are used instead of relying on a clinical diagnosis.

The present meta-review is subject to certain limitations, the main one is that our search may not have identified all published SRs on pesticide exposure and the target neurological outcomes during the search period. Likewise, it was beyond the scope of this review to examine the individual studies addressing those outcomes. In contrast, we intended to tackle a new approach to go a step beyond evaluating quality of SRs to integrating epidemiological evidence into risk assessment.

4.3. Implications of SRs for risk assessment

In the last few years, regulatory agencies (US-EPA and EFSA) are committed to incorporate observational epidemiological studies on potential long-term adverse health effects from pesticide use in the risk assessment process. In particular, SRs of observational studies provide information that strengthens the understanding of the potential hazards of pesticides, exposure-response characterization, exposure scenarios and methods for assessing exposure, and ultimately risk characterization (van den Brandt, 2002).

The quality and relevance of epidemiological research should be considered when selecting epidemiological studies from the open literature to be included in a SR and further use in risk assessment. Core criteria for this purpose include: a) adequate assessment of exposure, preferentially by reporting biomarker concentrations (mean, percentiles, range) in standardized units which will allow for a dose–response trend; b) reasonably valid and reliable outcome assessment (well defined clinical entities or validated surrogates); c) data on the magnitude of the association between exposure and health outcomes; d) results stratified by study design (cohort, case–control, cross-sectional studies) before being pooled; e) to adequately account for potentially confounding variables (including exposure to multiple chemicals); and f) subgroup or subpopulation analysis (e.g., gender, age, ethnicity). Besides, synthesis of evidence must be supported by biological plausibility and research gaps should be identified and reported.

Epidemiological studies can contribute to risk assessment in a variety of ways. Consistency of results across studies, particularly for long-term health outcomes, supports the specificity of the association and can be relevant for hazard identification, the first stage of the risk assessment process. Thus, higher confidence should be given to results which are replicated in multiple studies and/or different populations. Besides, outcomes reported in these studies can be compared qualitatively with those seen in vitro and animal studies to evaluate biological plausibility or human relevance of animal findings (Hertz-Picciotto, 1995). Thus, epidemiological studies provide complementary data to toxicological in vivo and mechanistic (in vitro or in silico) studies as part of the overall weight of evidence of the available data using modified Bradford Hill criteria as an organizational tool (US-EPA, 2010). Therefore, epidemiology increasingly contributes to establishing causation (Buonsante et al., 2014). Epidemiological studies also support the correlation between humans' low-dose exposures and diseases, avoiding the uncertainty associated in extrapolation across species. Although most epidemiological studies present limitations in exposure assessment or data analysis that makes them less useful for quantitative risk assessment, they can still be useful for hazard identification. Only high quality studies with robust and quantitative exposure assessment can be used to estimate risk quantitatively (Calderon, 2000). These studies can be used to compare with points of departure derived from experimental animal studies conducted for regulatory purposes. When these human studies are more sensitive than animal studies, they can be categorized as "quantitative" and may be used for establishing a point of departure for risk assessment (US-EPA, 2010 and 2012).

Moreover, as epidemiological studies involve actual real-world exposures and provide insight on actual chemical exposures in humans, they avoid the need of high dose extrapolation as occurs with animal testing (US-EPA, 2010). In addition, epidemiological data include the genetic diversity and variability inherent to human populations, thus better representing actual population response to environmental chemicals than laboratory animals (Calderon, 2000). When animal and human data show a similar toxic profile, both quantitatively and qualitatively, there is high confidence in the human health risk assessment (US-EPA, 2010).

4.4. Recommendations for a better use of SRs in risk assessment

The large amount of data collected and extracted in SRs, particularly in relation to the characterization of exposure and adverse effects, should be briefly summarized and discussed properly to facilitate drawing sound conclusions. Quantitative data should be expressed in

Table 6
Summary of exposure assessment and major results of SRs evaluating Alzheimer's disease (AD) from exposure to pesticides.

Author (year)	Type of exposure assessment			Exposure levels	Results	Analysis for confounders	Stratification by sex/gender	Sample size (n)	Usefulness for risk assessment
	Q	B	JEM						
Sanborn et al. (2007)	–	–	–	Not reported	1/2 articles found a significant association in men (ORs not reported in the SR) 1/2 articles did not found any significant association	Not reported in the SR	Not reported	Not reported	For problem formulation and hazard identification No meta-analysis was reported
Santibáñez et al. (2007)	3/6	–	3/6	Not reported	2/6 articles found significant associations between occupational exposure to pesticides and AD: a) aRR 4.35 (95%CI 1.05–17.90) to defoliants and fumigants (but a smaller and non-significant association to pesticides/fertilizers aRR 1.45 (95%CI 0.57–3.68)); n = 694 b) aRR 2.39 (95%CI 1.02–5.63) to pesticides in men (non-significant in women aRR 0.89 (95%CI 0.49–1.62)) 4/6 articles found non-significant associations	5/6 articles adjusted for confounding variables 1/6 articles did not adjust for confounding variables	1/6	706 cases and 2966 controls	For problem formulation and hazard identification No meta-analysis was reported

AD: Alzheimer's disease; B: biomarkers; JEM: Job-exposure matrix; Q: questionnaire; RR: relative risk; RRa: adjusted relative risk.

standardized units for a better interpretation of results and to facilitate direct comparison with data across studies.

Statistical estimates (OR, RR or regression coefficients — β values) of non-significant results should not be extracted to avoid misunderstanding. One limitation of some SRs is not to indicate whether results are statistically significant or not. In the case of being significant, statistical estimates are not always explicitly expressed but merely mentioned in the text or shown in extraction tables by using arrows pointing up or down. This limitation precludes assessment of differences across SRs evaluating the same set of original studies. Moreover, when an association is statistically significant, data extraction tables should specify the change in effect size by unit of change in the exposure estimate. If, in addition, exposure and outcomes are uniformly defined and measured across studies, result comparability can be achieved.

When search dates and strategy, and/or inclusion/exclusion criteria vary across SRs on a given exposure-outcome pair, distinct evidence integration can be achieved leading to different qualitative or quantitative findings. Theoretically, if two or more SRs assess the same set of evidence they must come to the same conclusions. For this reason, transparency in the methodology used in a SR is of utmost importance.

When pesticide exposure is measured by means of biomonitoring data, it would be helpful to provide information regarding the particular levels to which the effect has been observed in order to identify whether those levels are associated with a higher or lower risk of developing the outcome of interest. This information may also contribute to human dose–response modeling.

5. Conclusions

The findings of this review on SRs published to date regarding the association between pesticide exposure and various neurological disorders reveal that current SRs can be used only for problem formulation and hazard identification. For this stage of risk assessment, quantified exposure data is not required. In the case of neurodevelopmental disorders, as quantitative data on exposure are partially available from large birth cohorts set up in the past decade, it is possible to go a step forward as these studies provide useful (although still scarce) information regarding exposure assessment. However, the major limitation of human neurodevelopmental studies is the lack of uniformity or homogeneity in the way that subtle adverse effects are evaluated. This limitation also precluded to carry out a meta-analysis in all the SRs published to date on the topic. Harmonization is needed with regard to exposure assessment, in particular quantitative data on exposure to a single pesticide should be provided by using human biomonitoring methods and expressing results with the same units. Outcomes should also be harmonized for an accurate and reproducible measurement. Only under this framework, data from human studies with similar designs can be merged to gain enough power to determine dose–response curves for risk assessment (e.g., benchmark dose modeling) which would allow points of departure to be derived.

In the case of PD and AD, the lack of quantitative measures of exposure to individual pesticides is an important drawback for using current SRs for human health risk assessment beyond hazard identification. Moreover, as neurodegenerative diseases have a long latency period, it can be anticipated that many years are needed before modern or next generation epidemiological studies with a prospective exposure assessment produce sound results for quantitative risk assessment. Although many of the SRs on PD, and to a lesser extent on AD, have carried out meta-analysis for the quantitative synthesis of data, their relevance for risk assessment modeling is still limited.

Meta-analyses are relevant for risk assessment because they increase the statistical power and precision for the effect of interest by pooling the results of all individual studies available. As meta-analyses determine the size of association averaged over the considered studies, they provide a stronger basis for hazard identification. However, meta-analytical approaches may be of limited value if a combined odds ratio is calculated based on meta-analyses interpreting exposure as a 'yes' or a 'no' because compounds subjected to exposure are not necessarily the same in all studies included. Even though in these cases meta-analyses may consistently show an increased risk associated with pesticide exposure, for risk assessment the exposure needs to be better characterized to disentangle the effect of specific pesticide classes or, even better, individual pesticides. Meta-analyses would be more informative for risk assessment if they present odds ratios for a given change in the continuous variable of exposure (or per a given percentile change in exposure) as this could be of help to derive health-based reference values. In case of substantial heterogeneity in the meta-analysis (largely due to inaccurate exposure characterization), the combined estimate may not be a meaningful description of the set of studies included in the meta-analysis. Sources of heterogeneity should be explored through stratification and/or meta-regression. Furthermore, meta-analysis techniques allow to examine the presence of diverse biases such as small study effects and excess significance bias. It is important to find models that adequately describe the effect-size distribution of the underlying population of studies. A higher quality of epidemiological research would allow for more robust SRs and meta-analyses, which can be then used to estimate more accurately the burden of disease related to pesticide exposure and further quantitative risk assessment.

Conflict of interest

The authors declare that there are no conflicts of interest.

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